

Clinical knots

The management of difficult anogenital warts

A McMillan

Patients with anogenital warts present the healthcare professional with two major problems—recurrence and persistence. These problems occur because of persistence of human papillomavirus in keratinocytes, defective immune responses in individuals with persistence and recurrence of warts, and the lack of specific antiviral therapy.

In this article, the discussion will be confined to the management of lesions visible to the naked eye and a scheme of management that I have found useful is shown in figure 1.

The hyperplastic condylomata acuminata that have been present for less than 3 months, often clear quickly after treatment with podophyllin, podophyllotoxin, or cryotherapy. Podophyllotoxin appears to be more effective than podophyllin in clearing warts and it has the added advantage that the patient can apply it. Recurrence, either at the site of the initial lesions or on adjacent skin or mucosa, is common,¹ and probably indicates active viral activity in that area; therefore, repeated cycles of treatment are often necessary before there is complete eradication. As surrounding tissue necrosis may be a problem, I do not use podophyllin or podophyllotoxin on warts in the vagina, anal canal, or on the uterine cervix. As lesions at these sites often regress spontaneously, I generally leave vaginal and anal warts untreated unless there are associated symptoms such as anorectal bleeding or troublesome vaginal discharge. In my hospital, laser therapy is used less frequently in the treatment of intravaginal or ectocervical warts but, although ulceration can be a complication, I have found 5-fluorouracil cream (5%) useful in the treatment of the former. Loop diathermy for ectocervical warts has the advantage that histological examination for cervical intraepithelial neoplasia (CIN) is possible, and this is my treatment of choice. Scissor excision under local or general anaesthesia is my preferred treatment for intra-anal warts.

Treatment with podophyllin or podophyllotoxin is less successful for sessile warts or lesions on dry skin surfaces, such as the shaft of the penis, and I prefer to treat these by ablative methods. Extensive hyperplastic anogenital warts are often refractory to podophyllin, podophyllotoxin, and cryotherapy and are best dealt with surgically or by the topical application of 5-fluorouracil cream, an agent that I have found particularly useful.

Persistence at the same site for at least 6 months despite regular conventional treatment is common and, in only very few cases, is a feature of immunodeficiency. A special case, however, is that of pregnancy when, with limited treatment options, anogenital warts can be

extensive and persistent. As regression often occurs within several weeks of delivery, treatment is usually unnecessary. Occasionally, however, the warts cause discomfort, and these may be treated with cryotherapy or trichloroethanoic acid (TCA). Conventional therapy is not uniformly successful in the treatment of warts in the immunocompromised patient, including HIV infected individuals, and immunotherapy is generally unsatisfactory; it is not, however, the purpose of this article to discuss this issue further.

In deciding on treatment of persistent lesions, it is worth considering the following:

Size and number of the lesions—Many individuals have a few warts that are less than 1 mm in diameter and reassurance that spontaneous regression will eventually occur, together with counselling about reducing the risk of sexual transmission, may be all that is necessary. In addition to the psychological morbidity, larger and more numerous warts, however, can cause discomfort, and, particularly at the urethral meatus and in the perianal region, they may bleed and become secondarily infected.

How the patient perceives his or her infection—Many patients seek some form of treatment because the presence of even the smallest wart causes considerable anxiety. Sometimes I find that talking with the patient about the following is all that is required:

- the benign nature of the lesions
- feelings of guilt about having acquired a sexually transmitted infection and allaying these
- the natural history of human papillomavirus infection
- treatment that is not curative
- the possible adverse effects of treatment of small lesions; there may be damage to surrounding, latent virus-containing tissue with the subsequent growth of warts at that site (Koebner phenomenon).

Many patients, however, are not satisfied by this approach.

What treatment, then, can be offered to the individual with persistent warts?

Ablative methods

Cryotherapy can be very successful in clearing warts that have failed to respond to podophyllin, and is my first line ablative method; perianal warts, however, do not respond so well. I have found scissor excision,² either under local or general anaesthesia, to be particularly helpful in the management of the latter and for sessile lesions of the labia majora and shaft of the penis. The results are generally good with little scarring at the excision site. Circumcision may be necessary in diabetic

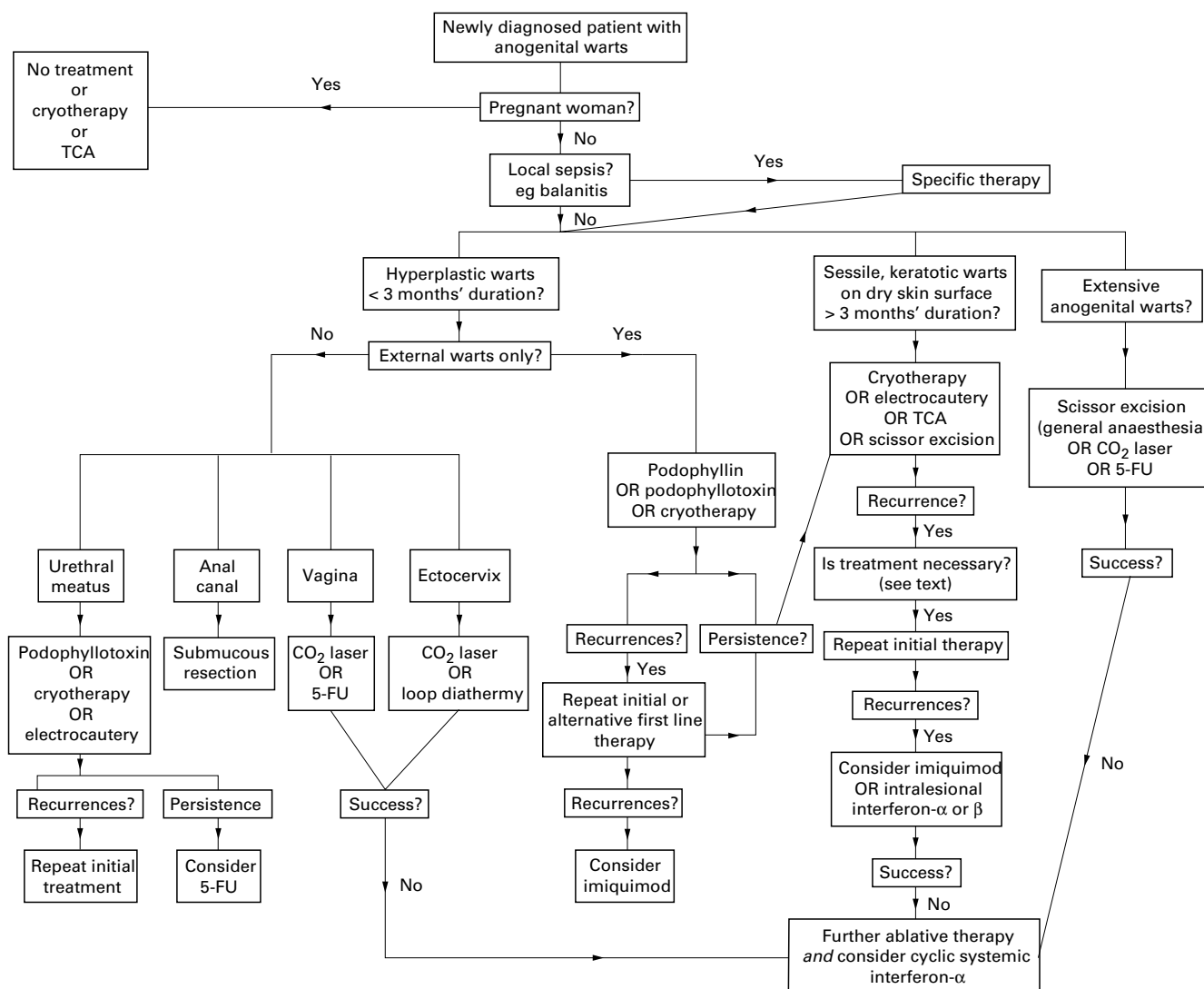


Figure 1 Flow chart of management of anogenital warts. TCA = trichloroethanoic acid, 5-FU = 5-fluorouracil cream (5%).

men with preputial warts and phimosis. Electrocautery and, where available, diathermy and laser therapy are alternative treatment methods but, if the lesions are extensive, there may be considerable pain at the operation site and the wounds may heal more slowly than after scissor excision.

The topical application of trichloroethanoic acid may be successful in the treatment of small persistent lesions, but painful ulceration may result, and I rarely use this agent.

I have found the topical application of 5-fluorouracil (5%) cream useful in the treatment of refractory condylomata of the urethral meatus and of the perianal area. Local adverse effects, particularly ulceration, are common and the patient should be warned about these.

Even with ablative methods, recurrence is not uncommon, and, if further ablative treatment fails, immunomodulatory therapy may be tried to reduce the risk of further recurrence.

Immunomodulatory therapy

Inosine pranobex was one of the first such agents to be used in clinical practice. While appearing in some trials to show some benefit, the place of inosine pranobex in the management of recurrent or persistent anogenital warts is still uncertain

Trials of interferons in the treatment of refractory warts have yielded conflicting results, and the place for such therapy is not well established.

SYSTEMIC INTERFERONS

Monotherapy with systemic interferon- α is ineffective.

INTRALESIONAL INTERFERONS

Small series of patients with refractory warts treated with intralesional interferon- α have shown a significant advantage over placebo in producing regression. In a placebo controlled trial of intralesional interferon- β given three times per week for 3 weeks, Dinsmore *et al*³ reported significantly better results with interferon than with placebo, with the complete disappearance of the treated warts or at least a 50% reduction in their area; this effect was particularly noted in women.

ADJUVANT THERAPY

Interferons have also been used as adjuvant to other therapy. Although some workers have shown significant benefit over placebo in patients given systemic interferon- α three times per week in addition to laser therapy, others have failed to show such advantage.

Adopting a different approach, Gross *et al*⁴ obtained reasonably good results with cyclic administration of interferon- α . Patients with refractory warts that had been treated with carbon dioxide laser were given daily subcutaneous injections of interferon- α , 1 MIU, in three cycles consisting of 5 days of therapy with a 4 week interval between each cycle. The recurrence rate in the interferon treated group was lower than that in the placebo group and it was concluded that such cyclic application of low dose interferon- α adjuvant to laser therapy was superior to continuous interferon treatment. As it has been shown that patients with warts that respond to interferon therapy already have enhanced cell mediated immune responses,⁵ it is unlikely that this form of therapy will be universally successful, irrespective of the mode of administration of interferon.

As the results of treatment with interferons, either alone or as adjunct therapy, are uncertain, as subcutaneous and intralesional injections are not always be acceptable to the patient, as therapy is expensive, and as there are frequent systemic side effects I only use these agents when all else fails and the patient demands further therapy. I have not been impressed with the outcome in the patients I have treated.

Imiquimod is an immune response modifier that has potent antitumour and antiviral activity. It induces interferon- α , interleukin 1 (IL-1), and tumour necrosis factor α (TNF- α) in peripheral blood, and human keratinocytes exposed to imiquimod show an increase in mRNA for IL-2, IL-6, and IL-8. Arany and Tying⁵ showed that wart clearance was associated with tissue production of interferons α , β , and γ , and TNF- α .

In a placebo controlled trial of imiquimod cream (5%), applied daily for a maximum of 16 weeks, Beutner *et al*⁶ reported a significant difference with respect to reduction in wart area

and clearance between those treated with imiquimod and those treated with placebo; this was particularly so in women. Of the patients who had complete wart clearance and who were followed up for 12 weeks, 19%, however, had recurrence. It is important to note, however, that this trial included individuals with previously untreated and treated warts. Erythema developed in the majority of individuals, but excoriation and erosion were found in fewer than 50% of imiquimod recipients.

Although these studies are encouraging, the place of imiquimod, alone or in combination with other agents, in the primary management of anogenital warts is as yet unclear, but it is an agent that I have used successfully when conventional therapy for persistent warts has failed.

Preliminary results of the treatment of anogenital warts with cidofovir and the retinoids are encouraging, and the results of ongoing clinical trials are awaited with interest. Interestingly, cidofovir may have a place in the management of warts in HIV seropositive patients.

- 1 Beutner KR, Wiley DJ. Recurrent external genital warts: a literature review. *Papillomavirus Report* 1997;8:69-74.
- 2 Thomson JPS. Perianal and anal condylomata acuminata. In: Smith R, Rob C, eds. *Operative surgery. Colon, rectum and anus*. London: Butterworths, 1977:376-8.
- 3 Dinsmore W, Jordan J, O'Mahony C, *et al*. Recombinant human interferon- β in the treatment of condylomata acuminata. *Int J STD AIDS* 1997;8:622-8.
- 4 Gross G, Roussaki A, Baur S, *et al*. Systemically administered interferon alfa-2a prevents recurrence of condylomata acuminata following CO₂-laser ablation. The influence of the cyclic low-dose therapy regimen. Results of a multicentre double-blind placebo-controlled clinical trial. *Genitourin Med* 1996;72:71.
- 5 Arany I, Tying SK. Activation of local cell-mediated immunity in interferon-responsive patients with human papillomavirus-associated lesions. *J Interferon Cytokine Res* 1996;16:453-60.
- 6 Beutner KR, Spruance SL, Hougham AJ, *et al*. Treatment of genital warts with an immune-response modifier (imiquimod). *J Am Acad Dermatol* 1998;38:230-9.